FDA U.S. FOOD & DRUG ADMINISTRATION

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ISSUES FOR
DRUG INDUCED LIVER INJURY
GUIDANCE REVISION

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Guidance

The guidance on Pre-marketing evaluation of drug-induced liver injury is clear that its major intent:

> distinguishing drugs with the potential for causing severe
> liver injury from the many drugs that cause visible but
> reversible injury, such as statins, tacrine, heparin, aspirin

The guidance focuses on drugs with primarily hepatocellular injury, although other kinds of injury such as obstructive or inflammatory effects can be important. As all know, the principal method for identifying severe injury potential is determining whether "Hy's Law" criteria are met; because with great consistency drugs that have even a few such cases have proved to cause fatal liver injury, including

> bromfenac, troglitazone (approved then withdrawn)
> ximelagatran, dilevalol, ximelagatran; approved in Europe
> (not in US) and withdrawn because of hepatotoxicity

Guidance (cont)

The guidance focuses on pure hepatocellular injury, to which Hy's Law criteria apply. Once there are other components, such as obstruction, interpretation is more complicated, but such drugs do exist (perhexiline, benoxaprofen) and their injuries can be serious.

Hepatocellular injury, even for drugs with potential for severe injury, in a typical drug development program, will generally not cause cases of fatal or near-fatal injury because these are very rare, probably because such drugs would be too hepatotoxic to proceed in development. Even for the hepatotoxins removed from the market, which usually cause such injury at a rate of 1 in 5-10,000 or less. What Hy's Law allows is interpretation of a lesser (not severe) injury that predicts the potential for more severe injury. It also enables us to distinguish drugs that cause mild hepatocellular injury (transaminase elevation) but do NOT have a risk of severe injury.

Hy's Law

What led to our current practice is Zimmerman's observation that a pure hepatocellular injury that damages enough liver to impair the function (ability to excrete bilirubin) has damaged a lot of the liver, probably more than 50%. Despite the liver's great regeneration ability, 50% destruction will leave some patients unable to recover; thus Dr. Zimmerman found that patients whose hepatocellular injury led to jaundice, had a 10-50% mortality rate. Thus, when a drug causes elevated transaminase, indicating liver injury, we now conclude that accompanying elevation of bilirubin to greater than 2x ULN represents major liver damage and a mortality risk of about 10% or greater.

Hy's Law

1. Excess of AT elevation to > 3x ULN compared to control

   These elevations are seen in all groups, but hepatotoxins always have more, sometimes much more, but it is not above a predictor of serious injury potential because many drugs not severely hepatotoxic show this (statins, tacrine, heparin).

2. Marked elevation in some patients to 5x, 10x, 20x ULN. These too can be seen with some non-hepatotoxic drugs (tacrine).

Hy's Law (cont)

3. One or more cases of elevated bilirubin to 2x ULN in setting of pure hepatocellular injury with no other explanation, i.e., no evidence of obstruction, no pharmacologic explanation, no concomitant illness (viral, alcohol, autoimmune hepatitis). In sum, the AT elevation and elevated bilirubin should have no other plausible explanation. **This last part of Hy's Law is not always appreciated but is critical. It goes beyond the familiar display of ALT and total bilirubin to the more difficult question of <u>causality.</u>**

    To date, we know of no false positive.

Problem

The criteria are strict (but perhaps not always easy to define) about assuring a lack of alternative explanations for decreased liver function, such as pre-existing disease or obstructive disease, but this means that we have no described way to analyze potential for severe hepatotoxicity for patients with pre-existing liver disease. Such people to date do not seem more vulnerable to drug hepatotoxicity, but could perhaps have diminished liver reserve, increasing risks of a hepatotoxic drug.

Problem (cont)

Probably more important, in some conditions, e.g., treatment of hepatitis, all patients will have pre-existing disease and current procedures do not provide a way to assess hepatotoxicity of drugs in those settings.

So, we should be interested in what adjustments to Hy's Law we could make to evaluate hepatotoxicity in patients with pre-existing liver disease. E.g., even if bilirubin is no longer reliable because of possible obstruction, are there other functional measures that could be useful?

Where to Go

One possibility, for known hepatotoxins, is to examine the subset of patients with pre-existing disease, to see if any signals were present that might have predicted hepatotoxicity.

Another area of interest is to look more closely at databases for hepatotoxins with more complex mechanisms, where a pure AT elevation will not be likely (benoxaprofen, perhexiline) for indicators of risk. Many drugs that cause biliary obstruction lead only to reversible hyperbilirubinemia. Can we distinguish these from perhexiline and benoxaprofen?